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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/511,657	DRUMM ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-23* is/are pending in the application.

4a) Of the above claim(s) *2,12,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11,13,15,16 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 10-12-06 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 7-12-06 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 10-12-06, claims 1–13 and 15–23 are pending in the application. Claims 2, 12, 17, and 18 remain withdrawn. Claims 1, 3-11, 13, 15, 16, and 19–23 are currently under examination.

This application contains claims that are drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

This application claims benefit to provisional application No. 60/431,173, filed on 12/5/2002, in a language other than English. An English translation of the non-English language provisional application and a statement that the translation is accurate must be filed in provisional application No. 60/431,173. See 37 CFR 1.78(a)(5). The English translation and a statement that the translation is accurate required by 37 CFR 1.78(a)(5) is missing. Accordingly,

applicant must supply 1) the missing translation and statement in provisional application No. 60/431,173 and 2) in the present application, a confirmation that the translation and statement were filed in the provisional application. If 1) and 2) are not filed (or the benefit claim withdrawn by the filing of an amendment or Supplemental Application Data Sheet) prior to the expiration of the time period set in this Office action, the present application will be abandoned. See 37 CFR 1.78(a)(5)(iv).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-11, 13, 15, 16, and 20-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 5-13, 16, 21, 44, and 47 of copending Application No. 10/511656. Although the conflicting claims are not identical, they are not patentably distinct from each other because conflicting Application No. 10/511656 claims a method for the specific modulation of the expression of target genes in cells

and/or tissues of the CNS and/or eye, wherein a composition comprising one or more double-stranded oligoribonucleotides (dsRNA)is introduced into a cell, tissue or organism outside the blood-brain or blood-retina barriers. Also claimed are embodiments thereof wherein the dsRNA molecules are between 21 and 23 nucleotides in length, and wherein the dsRNAs are applied outside the eyeball by iontophoresis, retrobulbar, or systemic application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

The Examiner notes that Claim 11 is indicated as "withdrawn" in the claim listing submitted by applicants on 10-12-06. However, claim 11 cannot be withdrawn, as it recites elected subject matter: antagonists or inhibitors derived from a nucleic acid molecule.

Applicants are requested to 1) correct the status identifier of claim 11 and amend claim 11 to cancel non-elected subject matter such as polypeptide, antibody, and ligand binding molecule; or 2) maintain the current status identifier and cancel elected subject matter such as a nucleic acid molecule.

Claim 19 is objected to because the claim recites a method according to claim 1, wherein said gene or a cDNA thereof comprises a nucleotide sequence or encodes an amino acid sequence selected from SEQ ID NO:3. A review of the sequence listing filed with the application on 10/18/2004 shows that SEQ ID NO:3 corresponds to a DNA nucleic acid sequence. Although an amino acid translation is provided in the sequence listing for SEQ ID NO:3, the sequence

listing identifies SEQ ID NO:3 as DNA; therefore, the Office's database has archived SEQ ID NO:3 as a nucleic acid sequence, not an amino acid sequence.

Removing references to amino acid sequence in claim 19 would overcome this objection.

Claim Rejections - 35 USC § 112—withdrawn

The rejection of Claims 7 and 14-16 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicants' amendments to the claims.

In the previous Action, it was stated that, in view of the indefiniteness of claim 14, dependent claims 15 and 16 could not be further treated on the merits.

However, with the amendment of 10/12/06, claims 15 and 16 are now definite and are therefore examined herein.

Claim Rejections - 35 USC § 112—maintained

Claims 1, 3-11, 13, and 20-23 remain rejected and claims 15 and 16 are now rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

As now amended, Claim 1 is drawn to a method for the treatment of a disorder of the central nervous system and/or eye comprising administering to a subject a composition

comprising a compound capable of modulating a target gene or gene product in a therapeutically effective amount, wherein said compound comprises a dsRNA. Claims 3-4 are drawn to methods thereof wherein the disorder is related to the eye, angiogenesis, neovascularization, retinal pigment epithelium, neurosensory retina, choriodea, macular degeneration, or diabetic retinopathy. Claims 7, 8, and 21-23 specify the route of administration, while claims 9–11 and 20 specify that the compound is a nucleic acid inhibitor or antagonist of the target gene or gene product. Claim 13 limits the invention to an inhibitor that consists substantially of RNA. Claims 15 and 16 limit the invention by stating that the dsRNA is between 21 and 23 nucleotides in length and that the dsRNA contains a 3'-hydroxyl group.

The claims remain broad. While the amendment narrows the scope of the invention to methods using dsRNAs, the genus of dsRNAs needed to practice the full scope of the claimed invention is extremely large, since to practice the claimed invention one of skill must be able to envision the structures of the dsRNAs for treating each of the disorders. Thus, the claims encompass a large genus of methods requiring a multitude of dsRNA compounds for modulating (inhibiting or upregulating) any gene in any species associated with a disorder of the CNS or eye.

Adequate written description support under 35 USC §112, first paragraph, does not exist for the genus of dsRNAs and compositions thereof required to practice the full scope of the invention now claimed. The specification discloses neither a representative number of species compounds nor any structure/function correlation that would enable one of skill to immediately envision the genus of dsRNAs and siRNAs for targeting the genus of genes associated with CNS and eye disorders in any organism.

A review of the instant application fails to find a description of the genes that are to be targeted by the instant methods such that one of skill could reasonably envision the structures of the dsRNAs needed to target these genes. Furthermore, Applicants have not pointed to or provided any evidence that the chemical and/or physical structures of the genes associated with any CNS or eye disorder in any species are described in the prior art or in the instant application. Logically, one cannot describe the dsRNAs, and, thereby, the methods of the instant invention without describing the gene targets. While the instant application provides a laundry list of genes at pages 55-58, there is no evidence or disclosure clearly linking the genes with any CNS or eye disorder, and no indication that modulating these genes with dsRNA will treat any of the currently recited disorders.

Apart from GFP, and the gene targets SEQ ID NO:1 and 2 (see page 18 of specification), a review of the specification fails to find any description, by words, structures, figures, diagrams, or formulas, of a representative number of dsRNA species nor any feature common to the genus that may be used in the instant methods to treat any CNS or eye-related disorder. While the specification teaches at pages 52-54 that dsRNA targeting GFP may be delivered to the retina of a transgenic mouse via intravenous injection and that GFP expression in the retina may be reduced by systemic delivery in a mouse, this example is not directed to the treatment of any eye or CNS disorder and does not describe any dsRNA or siRNA or any vector thereof, nor any other molecule for use in the instant methods to treat an eye or CNS disorder. And while pages 55-58 list several genes, there is no disclosure explaining the relevance of these genes to any particular disorder nor any description of the compounds that are to be used to inhibit or agonize these genes so as to provide a definitive treatment effect. While these genes may indeed be suitable

targets for a given disorder, even if one knew which gene was related to any given disorder and whether or not to inhibit or agonize the gene or gene product, one of skill in the art would, nevertheless, be left to de novo screening methods to identify the dsRNAs having the desired activity to produce the desired therapeutic effect.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of those specific, structurally and functionally defined targets, such as SEQ ID NO:3, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of all gene targets associated with CNS and eye disorders; thus, one of skill cannot envision the chemical and physical structure of dsRNAs and siRNAs needed to modulate all such targets, which is required to practice the claimed methods for treating each of the disorders delineated in the claims, regardless of the complexity or simplicity of the method used to screen for and identify such compounds. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.
>
> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

In the instant case, the specie(s) specifically disclosed is/are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision.

(See page 1115.)

Accordingly, the instant claims remain rejected for lack of written description support.

Response to Arguments

Applicants argue that as amended the claims recite dsRNAs, and that dsRNAs provide specific structural and functional guidance to one of ordinary skill to envision the genus of compounds needed to practice the claimed methods (Remarks, page 5).

Applicant's arguments filed 10-12-06 have been fully considered but they are not persuasive.

As explained above, the claims remain extremely broad, encompassing a large genus of dsRNAs for treating virtually any CNS or eye disorder in any organism. Adequate written description does not exist in the instant application for the complete genus of dsRNAs needed to practice these methods because the instant application does not adequately describe the genes that art to be modulated with the instant methods. One cannot describe a method of modulating gene expression in a cell using dsRNAs and/or siRNAs without describing the nucleic acid targets.

Accordingly, the instant claims remain rejected for lack of written description support.

Claim Rejections - 35 USC § 103—New

Claims 1, 3-11, 13, 15, 16, and 19–23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al. (US Patent 5,814,620); Dryja et al. (US Patent 5,498,521), Weber et al. (1991) *Nucleic Acids Res.* 19:6263-6268; Epstein (1998) *Methods: A Companion to Methods in Enzymology* 14:21-33; Elbashir et al. (2001) *Nature* 411:494-498; and Bass (2001) *Nature* 411:428-9.

With the amendment of 10-12-06, the claims are now generally drawn to methods of treating CNS and eye disorders using dsRNAs such as siRNAs.

Robinson et al. teach a method for treating diabetic retinopathy and macular degeneration comprising the step of intravitreally administrating to a subject afflicted with diabetic retinopathy a therapeutic amount of an antisense oligonucleotide specific for vascular endothelial growth factor nucleic acid and effective in inhibiting the expression of vascular endothelial growth factor in the retina, including choroidal neovascularization (claim 1 and Examples 4 and 5, column 15, for example). Several representative embodiments of anti-VEGF oligonucleotides are disclosed at Table 1, column 6). The antisense oligonucleotide may be composed of ribonucleotides, deoxyribonucleotides, or a combination thereof (column 7, lines 30-35; claim 5). They may be combined with a variety of pharmaceutically acceptable carriers and formulated in pyrogen-free compositions in a way suitable for intraocular or intravitreal or systemic administration (column 10, lines 20-40; column 11, lines 5-15). For example, the antisense oligonucleotide may be formulated as a sterile, buffered, isotonic solution (column 10, lines 20-35).

Robinson et al. further teach methods for delivering antisense oligonucleotides intraoculary to cells in the eye to treat diseases associated with the eye. Robinson et al. teach specifically methods for targeting VEGF in retinal cells using intravitreal administration of antisense oligonucleotides targeting VEGF. Robinson et al. do not teach antisense oligonucleotides or vectors expressing oligonucleotides targeting SEQ ID NO:3.

Robinson et al. do not teach dsRNAs or siRNAs for modulating genes associated with eye disease.

The instant application teaches that SEQ ID NO:3 corresponds to the beta-subunit of rod cGMP phosphodiesterase corresponding to GenBank Accession No. NM_000283 (page 18), which is 3283 nucleotides in length. A standard search of SEQ ID NO:3 finds that SEQ ID NO:3 corresponds to GenBank Accession No. S41458, which is 3231 nucleotides in length (see search result in Exhibit A, provided with the Action of 7-12-06). A comparison of NM_000283 and S41458 shows that NM_000283 comprises S41458 (compare Exhibits B and C, provided with the Action of 7-12-06).

Weber et al. teach the full length sequence of rod cGMP phosphodiesterase corresponding to GenBank Accession No. NM_000283 (See Exhibit C, provided with Action of 7-12-06).

Dryja et al. teach methods diagnosing in a mammal, e.g., a human subject, an increased likelihood of, inclination toward, or susceptibility to developing a disease, e.g., retinitis pigmentosa, in which a mutant form of a human photoreceptor protein is a causative agent. Human photoreceptor proteins said to be potential causative agents include the beta subunit of rod retinal cGMP phosphodiesterase (column 2, top). Dryja et al. teach that mutant photoreceptor proteins such as cGMP phosphodiesterase may be involved in hereditary retinal degenerative diseases in which progressive, bilateral degeneration of retinal structures leads to loss of retinal function; these diseases include, for example, age-related macular degeneration (column 1).

In an exemplary embodiment, Dryja et al. teach antisense probes that may be used to diagnose the presence and relative quantity of the beta subunit of rod retinal cGMP

phosphodiesterase corresponding to the gene disclosed by Weber et al. (see Example 9, column 15, lines 35-45), which, as explained above, also corresponds to SEQ ID NO:3. It was found that patients with mutations in the PDE .beta. gene had clinical findings typical of retinitis pigmentosa (column 17, top). Accordingly, Dryja et al. suggest that the expression of a mutant form of the protein encoded by SEQ ID NO:3 is associated with a disorder of the eye.

Epstein et al. teach the use of antisense inhibitors for specifically regulating phosphodiesterase genes, both *in vitro* and *in vivo*. It is taught for example that the goal of antisense technology is to develop small oligonucleotides, plasmids, or retroviral vectors that can be introduced into cells in order to inhibit gene products specifically. Epstein et al. teach that antisense oligos can be used to inhibit essentially any isoform of PDE (page 21). Epstein et al. provide a complete blueprint for the design and preparation of antisense oligonucleotides against the known PDE gene sequences (see pages 22-25). Epstein et al. state that a number of excellent reviews have been written recently that describe the characteristics of the different PDE isoforms, their regulation, function, and progress in development of pharmacological inhibitors of PDE as therapeutic agents (page 21, 2nd column). Epstein et al. cite a number of additional references as support therein.

Elbashir et al. teach that siRNAs (21-nt RNA duplexes) specifically suppress the expression of endogenous and heterologous genes in different mammalian cell lines, including HeLa cells. It is taught that siRNAs provide a tool for studying gene function and may eventually be used as gene-specific therapeutics (pages 494 and 497). Elbashir et al. provide a number of different working examples, showing sequence-specific, reproducible knockdown of different transgenes and endogenously expressed genes in mammalian cells, using structurally defined

siRNAs (see Figs. 1, 2, 3, and 4, for example). It is taught that siRNAs are extraordinarily powerful reagents for mediating gene silencing, and that siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene-targeting experiments (page 496).

Bass teaches that, like some antisense oligonucleotides, which trigger RNase H-catalyzed cleavage of their targets, siRNAs trigger the degradation of complementary messenger RNAs (page 428 and Fig. 1). A general outline of the RNAi mechanism is taught, showing how siRNA-mediated RNAi may be used to interfere with gene expression using siRNAs directed against specific mRNA sequences (Fig. 1). Bass teaches that RNAi has repeatedly proven itself to be more robust that antisense techniques: it works more often, and typically decreases expression of a gene to lower levels, or eliminates it entirely. Furthermore, siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments.

Thus, the prior art teaches, in general, that siRNAs and antisense oligonucleotides can be used to produce the same effect, albeit with different potencies and by different biochemical mechanisms. siRNAs and antisense oligos can both be used to inhibit gene expression *in vivo* or *in vitro*, via mRNA degradation or translation attenuation, and, thus, both types of nucleic acids may be used to prevent the expression of a gene in a cell. For example, Bass teaches that antisense RNA is another technique to prevent the expression of particular genes (page 429). Thus, in this sense, siRNAs and antisense oligos are art-recognized equivalents that may be used for the same purpose: reducing or inhibiting gene expression. (See for example MPEP §2144.06, SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE.)

Nevertheless, as explained above, siRNAs possess certain advantages over antisense oligos, which would motivate one of ordinary skill in the art to select siRNAs over antisense oligos to more efficiently block and/or reduce the expression of any given target gene, particularly a gene known to be involved in cancer.

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to use siRNAs, as taught by Elbashir et al. and Bass, for inhibition of SEQ ID NO:3, corresponding to beta subunit of rod cGMP phosphodiesterase to inhibit the expression of mutant isoforms of SEQ ID NO:3 and consequent development of ocular diseases associated with the expression of mutant isoforms of SEQ ID NO:3.

One would have been both well motivated and have had a reasonable expectation of success given that Dryja et al. teach that mutant isoforms of beta phosphodiesterase (i.e., SEQ ID NO:3) may predispose individuals to macular degeneration, and given that Robinson et al. teach that antisense compounds may be used effectively in retinal cells specifically to inhibit the expression of genes associated with macular degeneration, and given that Epstein teaches that antisense compounds may be used effectively to inhibit the expression of phosphodiesterases in particular. Given that Elbashir et al. and Bass teach that siRNAs are in general more potent than antisense oligonucleotides for reducing gene expression in cells, one of skill would have been motivated to substitute siRNAs for antisense oligonucleotides in the methods of Dryja et al. and/or Epstein et al. to silence the expression of genes such as SEQ ID NO:3 associated with eye disorders.

One would have had a reasonable expectation of success in targeting mutant forms of SEQ ID NO:3 as well as SEQ ID NO:3 itself given that Dryja et al. teach both the wild type

form, as disclosed in Weber et al., and common mutations thereof leading to eye-related disease (see example 9).

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicants' Arguments

Applicants' arguments presented on 10-12-06 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Prior art made of record but not currently relied on

The following prior art is made of record and is not relied upon, but is considered pertinent to applicant's disclosure.

Collins et al. (1992) "The human beta-subunit of rod photoreceptor cGMP phosphodiesterase: complete retinal cDNA sequence and evidence for expression in brain" *Genomics* 13 (3): 698-704. Collins et al. show a full length cDNA sequence that is 100% identical to instant SEQ ID NO:3, now recited in claim 19 (see alignment below). Collins et al. teach that the molecular cloning of the cDNA encoding for the PDEB represents the first step in establishing whether this gene plays a causative role in any one of the several human hereditary retinopathies.

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RESULT 3
S41458
LOCUS       S41458                 3231 bp    mRNA    linear   PRI 08-MAY-1993
```

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DEFINITION  rod cGMP phosphodiesterase beta-subunit [human, mRNA, 3231 nt].
ACCESSION   S41458
VERSION     S41458.1  GI:252252
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini;
            Hominidae; Homo.
REFERENCE   1  (bases 1 to 3231)
  AUTHORS   Collins,C., Hutchinson,G., Kowbel,D., Riess,O., Weber,B. and
            Hayden,M.R.
  TITLE     The human beta-subunit of rod photoreceptor cGMP phosphodiesterase:
            complete retinal cDNA sequence and evidence for expression in brain
  JOURNAL   Genomics 13 (3), 698-704 (1992)
   PUBMED   1322354
  REMARK    GenBank staff at the National Library of Medicine created this
            entry [NCBI gibbsq 109783] from the original journal article.
FEATURES             Location/Qualifiers
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                     SSFADELTDYKTKNMLATPIMNGKDVVAVIMAVNKLNGPFFTSEDEDVFLKYLNFATL
                     YLKIYHLSYLHNCETRRGQVLLWSANKVFEELTDIERQFHKAFYTVRAYLNCERYSVG
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                     QTMFTLLMTGKLKSYYTDLEAFAMVTAGLCHDIDHRGTNNLYQMKSQNPLAKLHGSSI
                     LERHHLEFGKFLLSEETLNIYQNLNRRQHEHVIHLMDIAIIATDLALYFKKRAMFQKI
                     VDESKNYQDKKSWVEYLSLETTRKEIVMAMMMTACDLSAITKPWEVQSKVALLVAAEF
                     WEQGDLERTVLDQQPIPMMDRNKAAELPKLQVGFIDFVCTFVYKEFSRFHEEILPMFD
                     RLQNNRKEWKALADEYEAKVKALEEKEEEERVAAKKVGTEICNGGPAPKSSTCCIL"
ORIGIN

  Query Match          100.0%;  Score 3231;  DB 5;  Length 3231;
  Best Local Similarity  100.0%;  Pred. No. 0;
  Matches 3231;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CTCCAGGGACAGGCAGCCACCATGAGCCTCAGTGAGGAGCAGGCCCGGAGCTTTCTGGAC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 CTCCAGGGACAGGCAGCCACCATGAGCCTCAGTGAGGAGCAGGCCCGGAGCTTTCTGGAC 60

Qy         61 CAGAACCCCGATTTTGCCCGCCAGTACTTTGGGAAGAAACTGAGCCCTGAGAATGTTGGC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 CAGAACCCCGATTTTGCCCGCCAGTACTTTGGGAAGAAACTGAGCCCTGAGAATGTTGGC 120
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Qy       121 CGCGGCTGCGAGGACGGGTGCCCGCCGGACTGCGACAGCCTCCGGGACCTCTGCCAGGTG 180
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       121 CGCGGCTGCGAGGACGGGTGCCCGCCGGACTGCGACAGCCTCCGGGACCTCTGCCAGGTG 180

Qy       181 GAGGAGAGCACGGCGCTGCTGGAGCTGGTGCAGGATATGCAGGAGAGCATCAACATGGAG 240
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Db       181 GAGGAGAGCACGGCGCTGCTGGAGCTGGTGCAGGATATGCAGGAGAGCATCAACATGGAG 240

Qy       241 CGCGTGGTCTTCAAGGTCCTGCGGCGCCTCTGCACCCTCCTGCAGGCCGACCGCTGCAGC 300
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       241 CGCGTGGTCTTCAAGGTCCTGCGGCGCCTCTGCACCCTCCTGCAGGCCGACCGCTGCAGC 300

Qy       301 CTCTTCATGTACCGCCAGCGCAACGGCGTGGCCGAGCTGGCCACCAGGCTTTTCAGCGTG 360
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Db       301 CTCTTCATGTACCGCCAGCGCAACGGCGTGGCCGAGCTGGCCACCAGGCTTTTCAGCGTG 360

Qy       361 CAGCCGGACAGCGTCCTGGAGGACTGCCTGGTGCCCCCCGACTCCGAGATCGTCTTCCCA 420
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       361 CAGCCGGACAGCGTCCTGGAGGACTGCCTGGTGCCCCCCGACTCCGAGATCGTCTTCCCA 420

Qy       421 CTGGACATCGGGGTCGTGGGCCACGTGGCTCAGACCAAAAAAGATGGTGAACGTCGAGGAC 480
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       421 CTGGACATCGGGGTCGTGGGCCACGTGGCTCAGACCAAAAAAGATGGTGAACGTCGAGGAC 480

Qy       481 GTGGCCGAGTGCCCTCACTTCAGCTCATTTGCTGACGAGCTCACTGACTACAAGACAAAG 540
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Db       481 GTGGCCGAGTGCCCTCACTTCAGCTCATTTGCTGACGAGCTCACTGACTACAAGACAAAG 540

Qy       541 AATATGCTGGCCACACCCATCATGAATGGCAAAGACGTCGTGGCGGTGATCATGGCAGTG 600
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Db       541 AATATGCTGGCCACACCCATCATGAATGGCAAAGACGTCGTGGCGGTGATCATGGCAGTG 600

Qy       601 AACAAGCTCAACGGCCCATTCTTCACCAGCGAAGACGAAGATGTGTTCTTGAAGTACCTG 660
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       601 AACAAGCTCAACGGCCCATTCTTCACCAGCGAAGACGAAGATGTGTTCTTGAAGTACCTG 660

Qy       661 AATTTTGCCACGTTGTACCTGAAGATCTATCACCTGAGCTACCTCCACAACTGCGAGACG 720
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       661 AATTTTGCCACGTTGTACCTGAAGATCTATCACCTGAGCTACCTCCACAACTGCGAGACG 720

Qy       721 CGCCGCGGCCAGGTGCTGCTGTGGTCGGCCAACAAGGTGTTTGAGGAGCTGACGGACATC 780
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       721 CGCCGCGGCCAGGTGCTGCTGTGGTCGGCCAACAAGGTGTTTGAGGAGCTGACGGACATC 780

Qy       781 GAGAGGCAGTTCCACAAGGCCTTCTACACGGTGCGGGCCTACCTCAACTGCGAGCGGTAC 840
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Db       781 GAGAGGCAGTTCCACAAGGCCTTCTACACGGTGCGGGCCTACCTCAACTGCGAGCGGTAC 840

Qy       841 TCCGTGGGCCTCCTGGACATGACCAAGGAGAAGGAATTTTTTGACGTGTGGTCTGTGCTG 900
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       841 TCCGTGGGCCTCCTGGACATGACCAAGGAGAAGGAATTTTTTGACGTGTGGTCTGTGCTG 900

Qy       901 ATGGGAGAGTCCCAGCCGTACTCGGGCCCACGCACGCCTGATGGCCGGGAAATTGTCTTC 960
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Db       901 ATGGGAGAGTCCCAGCCGTACTCGGGCCCACGCACGCCTGATGGCCGGGAAATTGTCTTC 960

Qy       961 TACAAAGTGATCGACTACATCCTCCACGGCAAGGAGGAGATCAAGGTCATTCCCACACCC 1020
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       961 TACAAAGTGATCGACTACATCCTCCACGGCAAGGAGGAGATCAAGGTCATTCCCACACCC 1020
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Qy       1021 TCAGCCGATCACTGGGCCCTGGCCAGCGGCCTTCCAAGCTACGTGGCAGAAAGCGGCTTT 1080
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1021 TCAGCCGATCACTGGGCCCTGGCCAGCGGCCTTCCAAGCTACGTGGCAGAAAGCGGCTTT 1080

Qy       1081 ATTTGTAACATCATGAATGCTTCCGCTGACGAAATGTTCAAATTTCAGGAAGGGGCCCTG 1140
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1081 ATTTGTAACATCATGAATGCTTCCGCTGACGAAATGTTCAAATTTCAGGAAGGGGCCCTG 1140

Qy       1141 GACGACTCCGGGTGGCTCATCAAGAATGTGCTGTCCATGCCCATCGTCAACAAGAAGGAG 1200
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Qy       1201 GAGATTGTGGGAGTCGCCACATTTTACAACAGGAAAGACGGGAAGCCCTTTGACGAACAG 1260
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Db       1201 GAGATTGTGGGAGTCGCCACATTTTACAACAGGAAAGACGGGAAGCCCTTTGACGAACAG 1260

Qy       1261 GACGAGGTTCTCATGGAGTCCCTGACACAGTTCCTGGGCTGGTCAGTGATGAACACCGAC 1320
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1261 GACGAGGTTCTCATGGAGTCCCTGACACAGTTCCTGGGCTGGTCAGTGATGAACACCGAC 1320

Qy       1321 ACCTACGACAAGATGAACAAGCTGGAGAACCGCAAGGACATCGCACAGGACATGGTCCTT 1380
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Db       1321 ACCTACGACAAGATGAACAAGCTGGAGAACCGCAAGGACATCGCACAGGACATGGTCCTT 1380

Qy       1381 TACCACGTGAAGTGCGACAGGGACGAGATCCAGCTCATCCTGCCAACCAGAGCGCGCCTG 1440
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Qy       1441 GGGAAGGAGCCTGCTGACTGCGATGAGGACGAGCTGGGCGAAATCCTGAAGGAGGAGCTG 1500
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1441 GGGAAGGAGCCTGCTGACTGCGATGAGGACGAGCTGGGCGAAATCCTGAAGGAGGAGCTG 1500

Qy       1501 CCAGGGCCCACCACATTTGACATCTACGAATTCCACTTCTCTGACCTGGAGTGCACCGAA 1560
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Db       1501 CCAGGGCCCACCACATTTGACATCTACGAATTCCACTTCTCTGACCTGGAGTGCACCGAA 1560

Qy       1561 CTGGACCTGGTCAAATGTGGCATCCAGATGTACTACGAGCTGGGCGTGGTCCGAAAGTTC 1620
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Qy       1621 CAGATCCCCCAGGAGGTCCTGGTGCGGTTCCTGTTCTCCATCAGCAAAGGGTACCGGAGA 1680
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Qy       1681 ATCACCTACCACAACTGGCGCCACGGCTTCAACGTGGCCCAGACGATGTTCACGCTGCTC 1740
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Db       1681 ATCACCTACCACAACTGGCGCCACGGCTTCAACGTGGCCCAGACGATGTTCACGCTGCTC 1740

Qy       1741 ATGACCGGCAAACTGAAGAGCTACTACACGGACCTGGAGGCCTTCGCCATGGTGACAGCC 1800
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Db       1741 ATGACCGGCAAACTGAAGAGCTACTACACGGACCTGGAGGCCTTCGCCATGGTGACAGCC 1800

Qy       1801 GGCCTGTGCCATGACATCGACCACCGCGGCACCAACAACCTGTACCAGATGAAGTCCCAG 1860
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             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1861 AACCCCTTGGCTAAGCTCCACGGCTCCTCGATTTTGGAGCGGCACCACCTGGAGTTTGGG 1920
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Qy       1921 AAGTTCCTGCTCTCGGAGGAGACCCTGAACATCTACCAGAACCTGAACCGGCGGCAGCAC 1980
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1921 AAGTTCCTGCTCTCGGAGGAGACCCTGAACATCTACCAGAACCTGAACCGGCGGCAGCAC 1980

Qy       1981 GAGCACGTGATCCACCTGATGGACATCGCCATCATCGCCACGGACCTGGCCCTGTACTTC 2040
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Qy       2041 AAGAAGAGAGCGATGTTTCAGAAGATCGTGGATGAGTCCAAGAACTACCAGGACAAGAAG 2100
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Db       2041 AAGAAGAGAGCGATGTTTCAGAAGATCGTGGATGAGTCCAAGAACTACCAGGACAAGAAG 2100

Qy       2101 AGCTGGGTGGAGTACCTGTCCCTGGAGACGACCCGGAAGGAGATCGTCATGGCCATGATG 2160
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Db       2101 AGCTGGGTGGAGTACCTGTCCCTGGAGACGACCCGGAAGGAGATCGTCATGGCCATGATG 2160

Qy       2161 ATGACAGCCTGCGACCTGTCTGCCATCACCAAGCCCTGGGAAGTCCAGAGCAAGGTCGCA 2220
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Db       2161 ATGACAGCCTGCGACCTGTCTGCCATCACCAAGCCCTGGGAAGTCCAGAGCAAGGTCGCA 2220

Qy       2221 CTTCTCGTGGCTGCTGAGTTCTGGGAGCAAGGTGACTTGGAAAGGACAGTCTTGGATCAG 2280
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Qy       2281 CAGCCCATTCCTATGATGGACCGGAACAAGGCGGCCGAGCTCCCCAAGCTGCAAGTGGGC 2340
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Db       2281 CAGCCCATTCCTATGATGGACCGGAACAAGGCGGCCGAGCTCCCCAAGCTGCAAGTGGGC 2340

Qy       2341 TTCATCGACTTCGTGTGCACATTCGTGTACAAGGAGTTCTCTCGTTTCCACGAAGAGATC 2400
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       2341 TTCATCGACTTCGTGTGCACATTCGTGTACAAGGAGTTCTCTCGTTTCCACGAAGAGATC 2400

Qy       2401 CTGCCCATGTTCGACCGACTGCAGAACAATAGGAAAGAGTGGAAGGCGCTGGCTGATGAG 2460
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Qy       2461 TATGAGGCCAAAGTGAAGGCTCTGGAGGAGAAGGAGGAGGAGGAGAGGGTGGCAGCCAAG 2520
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Qy       2521 AAAGTAGGCACAGAAATTTGCAATGGCGGCCCAGCACCCAAGTCTTCAACCTGCTGTATC 2580
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Qy       2581 CTGTGAGCACTGGTCCCGTGGGGACCCTATGGCTCCCTCAATCTTCACCCACTAGGATTT 2640
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Qy       2641 GGGTTCTGCCTGTGGCTATTTGCTACAAGAGGTTAGGAAGCCCAAGAAAATGACTGAAGA 2700
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Qy       2761 CACCCAGGCTGGAGTGCCGTGGCACGATCTCAGCTCACTGCAACCTCCACCTCCCAGGTT 2820
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Db       2761 CACCCAGGCTGGAGTGCCGTGGCACGATCTCAGCTCACTGCAACCTCCACCTCCCAGGTT 2820
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Qy       2821 CAAGCGATTCTCGTGCCTCAGCCTCCTGAGTAGCTGGGACTACAGGCGCCCACCACCACA 2880
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Qy       2881 CATGCTAATTTTTGTATTTTCAGTACAGATGGGGTTTCACCATATTGGGCAGGCTGGTCT 2940
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Db       2881 CATGCTAATTTTTGTATTTTCAGTACAGATGGGGTTTCACCATATTGGGCAGGCTGGTCT 2940

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Qy       3181 AGATGGACACAGGCCGTTTCTCATCCAGTTTAGGAAAACACACATGCTCAG 3231
             ||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       3181 AGATGGACACAGGCCGTTTCTCATCCAGTTTAGGAAAACACACATGCTCAG 3231
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Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571)272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Louis V. Wollenberger, Ph.D.
Examiner
Art Unit 1635

October 24, 2006

SEAN McGARRY
PRIMARY EXAMINER
1635